

**Clinical Laboratory Improvement Advisory Committee (CLIAC)
January 30-31, 2002 - Atlanta, GA**

Summary Report

Table of Contents

- I. Record of Attendance
- II. Clinical Laboratory Improvement Advisory Committee Background
- III. Call to Order and Committee Introductions
- IV. Presentations and Committee Discussion
 - Food and Drug Administration (FDA) Update
 - Division of Clinical Laboratory Devices (DCLD)
 - Blood Products Advisory Committee (BPAC) Meeting Report
 - CLIA-Unregulated Tests
 - Centers for Medicare & Medicaid Services (CMS) Update
 - Centers for Disease Control and Prevention (CDC) Update
 - CDC's Laboratory Response to the Recent Anthrax Events
 - Towards a National Laboratory System
 - New York State's Bioterrorism Experience
 - Waiver Recommendations
 - Unregulated Tests Workgroup Report
 - Public Comments
 - Quality Institute
 - Secretary's Advisory Committee on Genetic Testing (SACGT) Meeting Report
 - Manufacturers' Pre-market Clearance and Good Manufacturing Practices - In-vitro Diagnostics (IVD) Regulation Overview
 - Public Comments
 - Adjourn
- V. Addenda

Record of Attendance

Committee Members

Dr. Toby L. Merlin, Chair
Dr. Ed Baker, Executive Secretary
Dr. George Birdsong
Dr. Patricia Charache
Dr. Brenta Davis
Dr. Andrea Ferreira-Gonzalez
Dr. Ronald Gagne
Dr. Barbara Goldsmith
Ms. Cynthia Johns

Dr. Ronald Luff
Dr. Valerie Ng
Dr. Timothy O’Leary
Mr. Stewart Richardson
Dr. Lawrence Silverman
Dr. Lawrence Sturman
Dr. Roland Valdes
Dr. Alice Weissfeld

Ex Officio Members

Dr. Robert Martin
Dr. Steven Gutman
Ms. Val Coppola for Ms. Judith Yost

Liaison Representative

Ms. Kay A. Setzer, AdvaMed

Centers for Disease Control and Prevention

Ms. Nancy Anderson
Ms. Diane Bosse
Ms. Gail Bosley
Ms. Carol Bigelow
Dr. Joe Boone
Dr. Bin Chen
Ms. Carol Cook
Ms. Judy Delany
Ms. Sharon Granade
Dr. Tom Hearn
Dr. Ed Holmes
Ms. Jerri Holmes

Ms. Stacey Holt
Mr. Kevin Malone
Dr. Adam Manasterski
Dr. Jan Nicholson
Ms. Anne Pollock
Ms. Andrea Pratcher
Ms. Eunice Rosner
Mr. Darshan Singh
Dr. Shahram Shahangian
Mr. Howard Eric Thompson
Ms. Pam Thompson
Ms. Rhonda Whalen

Department of Health and Human Services (Agencies other than CDC)

Ms. Minnie Christian (CMS)	Ms. Cecelia Hinkel (CMS)
Ms. Clara Sliva (FDA)	Dr. Joe Hackett (FDA)
Dr. Elliot Cowan (FDA)	Dr. Donna-Bea Tillman (FDA)

CLINICAL LABORATORY IMPROVEMENT ADVISORY COMMITTEE

The Secretary of Health and Human Services is authorized under Section 353 of the Public Health Service Act, as amended, to establish standards to assure consistent, accurate, and reliable test results by all clinical laboratories in the United States. The Secretary is authorized under Section 222 to establish advisory committees.

The Clinical Laboratory Improvement Advisory Committee (CLIAC) was chartered in February 1992 to provide scientific and technical advice and guidance to the Secretary and the Assistant Secretary for Health regarding the need for, and the nature of, revisions to the standards under which clinical laboratories are regulated; the impact on medical and laboratory practice of proposed revisions to the standards; and the modification of the standards to accommodate technological advances.

The Committee consists of 20 members, including the Chair. Members are selected by the Secretary from authorities knowledgeable in the fields of microbiology, immunology, chemistry, hematology, pathology, and representatives of medical technology, public health, clinical practice, and consumers. In addition, CLIAC includes three ex officio members, or designees: the Director, Centers for Disease Control and Prevention; the Commissioner, Food and Drug Administration; the Administrator, Centers for Medicare & Medicaid Services (formerly, Health Care Financing Administration); and such additional officers of the U.S. Government that the Secretary deems are necessary for the Committee to effectively carry out its functions. CLIAC also includes a non-voting liaison representative who is a member of AdvaMed (formerly, Health Industry Manufacturers Association) and such other non-voting liaison representatives that the Secretary deems are necessary for the Committee to effectively carry out its functions.

Due to the diversity of its membership, CLIAC is at times divided in the guidance and advice it offers to the Secretary. Even when all CLIAC members agree on a specific recommendation, the Secretary may not follow their advice due to other overriding concerns. Thus, while some of the actions recommended by CLIAC may eventually result in changes to the regulations, the reader should not infer that all of the Committee's recommendations will be automatically accepted and acted upon by the Secretary.

CALL TO ORDER – INTRODUCTIONS/FINANCIAL DISCLOSURES

Dr. Toby Merlin, CLIAC Chair, called the meeting to order and welcomed the Committee members. Dr. Edward Baker, Director, Public Health Practice Program Office (PHPPO), Centers for Disease Control and Prevention (CDC), recounted the events of September 11, 2001, the subsequent incidents involving anthrax, and the consequential effects on the nation, CDC, and the CLIAC meeting scheduled for September 12-13, 2001, which was cancelled. He related CDC's role in providing support to the states during the challenging days and months following these events and pointed out the National Laboratory System (NLS) is moving from a concept to a reality, with help from many people. He appealed to CLIAC to give its strong support for the NLS at CDC. Dr. Robert Martin, Director, Division of Laboratory Systems (DLS), PHPPO, CDC, added his welcome to the Committee and explained he was in India at the time of the September 11 events assisting with the development of an integrated-laboratory system for disease surveillance. CLIAC members then made self-introductions and disclosure statements of their financial interests relevant to topics to be discussed during the meeting.

PRESENTATIONS AND COMMITTEE DISCUSSION

■ Food and Drug Administration (FDA) Update

Division of Clinical Laboratory Devices

Addendum A

Dr. Steven Gutman, Director, Division of Clinical Laboratory Devices (DCLD), Office of Device Evaluation (ODE), Center for Devices and Radiological Health (CDRH), FDA, updated CLIAC on FDA activities relevant to CLIA. He reviewed the status of FDA and DCLD personnel changes, summarized the workload levels for the 510(k) and the premarket approval (PMA) review processes, and discussed FDA's initiative relative to down-classifications of analyzers and tests. In addition, he provided information demonstrating that FDA has categorized more than 1,800 submissions received for test categorization and continues to work with other agencies on genetic initiatives, bioterrorism preparedness, and a task force to combat antimicrobial resistance. Dr. Gutman also addressed FDA's re-engineering plans to reduce burden, which include identifying ways to streamline the submission process and increasing flexibility by offering an expanded menu of submission choices. New options for test device review were presented, followed by a summary of FDA's strategic plan to ensure the health of the public throughout the total product life cycle.

Committee Discussion

One Committee member inquired about FDA's new options for test device review. Dr. Gutman replied these processes are evolving and FDA is asking professional groups for help, particularly with guidelines for the abbreviated 510(k) review. This review relies on the manufacturer's ability to use established standards, such as those contained in NCCLS's EP-05A document

(Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline); however, these standards need to be further defined. At present, these standards focus on laboratory practice rather than manufacturer practice.

Blood Products Advisory Committee Meeting Report

Addendum B

Dr. Elliott Cowan, Division of Emerging and Transfusion Transmitted Diseases, Center for Biologics and Research, FDA, reported on the June 14, 2001, Blood Products Advisory Committee (BPAC) meeting. At this meeting, BPAC was asked to consider whether FDA, in light of the known benefits and risks of rapid HIV testing, should waive simple and accurate HIV testing from CLIA under its draft waiver guidance. Fifteen members of the Committee voted against waiver of rapid HIV tests and two members abstained. BPAC further recommended that some oversight is needed for rapid HIV tests and pre- and post-analytic concerns such as counseling and confirmatory testing should be considered. The Committee unanimously voted in favor of pursuing other approaches under CLIA (e.g., limited public health testing) to promote wider access to rapid HIV testing. Since the June meeting, FDA has withdrawn its draft waiver guidance and is using the criteria listed in the September 1995 proposed rule for its waiver reviews. In closing, Dr. Cowan requested additional input from CLIAC on the criteria and process for waiver determinations.

Committee Discussion

- One CLIAC member, also present at the BPAC meeting, concurred with Dr. Cowan's summary and added there were impassioned pleas by some of the meeting's attendees to waive rapid HIV tests. However, many of these pleas were based on misconceptions of testing accessibility. In addition, CMS data presented at the meeting illustrated some of the problems occurring in laboratories performing waived testing, particularly related to failure to follow manufacturer's instructions. With this in mind, BPAC felt it would be impossible to control the quality of testing in non-traditional testing sites without some type of oversight, which would not occur if the testing was waived.
- Another CLIAC member noted a false positive or false negative HIV result would not only be devastating to an individual, it would also be a public health risk. Other members agreed and pointed out these same issues could apply to genetic testing.
- CLIAC members agreed that promoting the use of CLIA's limited public health testing exception is preferable to waiving these tests. This exception permits not-for-profit federal, state, or local government laboratories that engage in limited (that is, a combination of 15 moderately complex or waived tests) to file a single application for a CLIA certificate.

CLIA-Unregulated Tests

Addendum C

Dr. Donna-Bea Tillman, Division of Cardiovascular and Respiratory Devices, ODE, CDRH, FDA, summarized FDA's review process for respiratory and cardiovascular monitoring devices, which include pulmonary function tests, cardiovascular monitors, pulse oximeters, and

indwelling arterial sensors. These monitoring devices measure a variety of physiological parameters and are not addressed in the CLIA regulations. Dr. Tillman explained that, as part of the 510(k) review program, a manufacturer must provide performance testing studies to demonstrate a device is substantially equivalent to a predicate device. In an effort to assure consistency among devices, FDA encourages manufacturers to meet voluntary standards, such as International Organization for Standardization (ISO) and International Electrotechnical Commission (IEC) standards. In addition, the Quality System Regulation (QSR), also known as current good manufacturing practice (cGMP), requires design controls and design control validation to ensure the quality of the finished device.

Committee Discussion

- One member asked if respiratory and cardiovascular monitoring devices provide reference intervals or normal ranges. Another member asked whether the accuracy of these devices is comparable to traditional laboratory tests. One member expressed concern that some indwelling sensors are providing electrolyte values used for diagnostic purposes. Dr. Tillman replied that while the manufacturer's studies must include testing the device over the range of values you would expect to see, these devices do not indicate whether results are normal or abnormal--they only report a number. In general, these devices are not as accurate as traditional laboratory tests and this is reflected in the device labeling. They are intended to show trends, not to give absolute values.
- In response to a member's concerns about the accuracy of a device's results when, for example, some indwelling arterial sensors are left in place for a week or more and clotting may occur, Dr. Tillman stated the manufacturer must provide data to support the claims it makes in the device's labeling. If the manufacturer wants to make a change, such as in the time period a device may be used, it must submit validation data to support its new claim. Once approved, the labeling may then be revised to reflect the extended performance period. She added, FDA can address labeling, but cannot address the clinician who uses the device off-label.
- When asked how FDA handles problems with respiratory and cardiovascular devices, Dr. Tillman responded that FDA monitors post-market usage of these products through Medwatch. Also, companies are required to have a system in place for monitoring complaints and reporting problems to FDA.
- Dr. Merlin acknowledged the practical limitations of extending CLIA authority to this realm of testing. He noted that CLIA may not be the appropriate oversight program; instead, he suggested that professional organizations be encouraged to adopt and promote appropriate standards.

■ **Centers for Medicare & Medicaid Services (CMS) Update**

Proposed Qualification Requirements for Directors of Laboratories Performing High Complexity Testing

Addendum D

Ms. Valerie Coppola, Division of Outcomes and Improvement, Center for Medicaid and State Operations, CMS, announced that a Notice of Proposed Rule Making (NPRM) addressing revisions to and expansion of the qualification requirements by which an individual with a doctoral degree may qualify as a director of a laboratory performing high complexity testing was published in the *Federal Register* on December 28, 2001. She noted the public comment period ended January 28, 2002, and that CMS and CDC are working on development of a final rule for publication by the end of the year.

Committee Discussion

The Committee's discussion focused on the NRPM's proposed requirement at §493.1443(b)(3)(iii), which would allow an individual with an earned doctoral degree in a chemical, physical, biological, or clinical laboratory science and at least six years of laboratory training or experience or both, including two years directing or supervising high complexity testing, to serve as a director of a laboratory performing high complexity testing.

- Many members felt this proposed qualification route is a step backward and the specified experience inconsistent with the responsibilities for directors of high complexity testing listed in the CLIA regulations at §493.1445. Several members were concerned this pathway would result in a decrease in the standard of care.
- Many members also viewed this qualification pathway as requiring less documented laboratory experience and expertise than is required for certification by an HHS-approved board (another qualification pathway). Several members emphasized that board certification requires documentation of education, training, and experience and an examination that assesses knowledge and competencies. In addition, to maintain board certification, recertification is required, which involves documentation of continuing education. Whereas, the proposed requirement at §493.1443(b)(3)(iii) did not include a mechanism for validation of basic knowledge and skills, especially in clinical laboratory practice and management, and offered no incentive for individuals to update their knowledge base.
- Some members believed the proposed option would be in conflict with the more stringent director requirements (i.e., specialty-specific experience and training) proposed in the Notice of Intent; Genetic Testing under the Clinical Laboratory Improvement Amendments (65 FR 25928) published in the *Federal Register* on May 4, 2000, which may be included in the NPRM for genetics testing (in development). The Committee was reminded that any conflicts between proposed rules would be resolved as comments are considered and the rule-making finalized. Furthermore, CLIA's technical supervisor requirements for the various laboratory specialty areas address specialty-specific education and training.

- CLIAC members questioned why this option was included in the NPRM. Ms. Rhonda Whalen, DLS, PHPPO, CDC, explained its inclusion was in response to comments received following the publication of the earlier date extension regulations suggesting an alternative be developed to qualify individuals with a doctoral degree on the basis of laboratory training or experience instead of requiring board certification. In addition, this proposed alternative seeks to address two significant healthcare issues--workforce supply and its role in maintaining access to and delivery of services.
- CLIAC members were asked to consider the potential impact on the healthcare system if this option was removed in the final rule and whether enough individuals would qualify as directors of laboratories performing high complexity testing. Several members believed there would be sufficient numbers of high complexity laboratory directors without providing this qualification pathway. Others stated that personnel shortages and access to care should not be used as a basis for lowering standards.
- Some members noted that in the past decade, HHS-approved boards have developed a variety of non-traditional routes to attain certification, thus providing additional avenues for certification to more candidates. One member suggested CLIA laboratory and director demographics from the CMS database could be helpful in establishing the current workforce matrix and determining the potential impact of requiring board certification. There was general agreement that available data be carefully reviewed and considered in regard to workforce supply and laboratory quality.
- In closing the discussion, Dr. Merlin summarized the Committee's belief that the high complexity laboratory director requirements should be consistent with the respective responsibilities outlined in the CLIA regulations. In addition, CLIAC officially recommended the proposed qualification requirement at §493.1443 (b) (3) (iii) of the December 28, 2001, NPRM be deleted or at least modified to require a more formal mechanism for documenting laboratory expertise, including validation of skills in the broad area of high complexity laboratory testing and evidence of continuing education, as currently demonstrated through board certification.

Delegation of Authority for CLIA

Ms. Coppola reviewed the delegation of authority for the CLIA program, explaining that legal authority for CLIA was given to CMS by the Secretary of Health and Human Services (HHS) pursuant to the CLIA statute. CMS, in turn, established written agreements with CDC and FDA specifying the functions and responsibilities of each agency, as well as the disbursement of CLIA funding to each agency commensurate with the assigned functions and responsibilities. She described how the three agencies work together to draft and publish CLIA regulations, with implementation of a regulation delegated to a specific agency. As an example of the tri-agency cooperative effort, Ms. Coppola noted that although the final waiver rule is being developed by all three agencies, FDA will be responsible for its implementation.

Committee Discussion

- Several members inquired about the status of the genetics NPRM and the quality control(QC)/quality assurance(QA) final rule. Dr. Joe Boone, DLS, PHPPPO, CDC, informed the Committee the proposed genetics regulation is being drafted and the impact analysis still needs to be done. The goal is to publish the genetics proposed rule by the end of the year. Ms. Coppola stated the QC/QA rule is in the final stages of development. After agency clearance by CDC and CMS, it will be forwarded to HHS for department clearance.
- One member inquired about the status of a recommendation from a Cytology workgroup meeting suggesting the FDA PMA process use an interagency group, with the FDA as the lead, to determine individual workload labeling as part of the approval of cytology devices. Dr. Gutman indicated the suggested interaction would be helpful as FDA does not have experience in evaluating manual workload associated with instrumentation.

■ **Centers for Disease Control and Prevention (CDC) Update**

CDC's Laboratory Response to the Recent Anthrax Events

Addendum E

Dr. Janet Nicholson, Associate Director for Laboratory Science, National Center for Infectious Diseases (NCID), CDC, provided an overview of the agency's laboratory bioterrorism response activities, which began October 13, 2001, with the second identified case of anthrax. She described the operational oversight, staffing, and organizational design of the Emergency Operations Center (EOC) that was established to coordinate preparedness and response activities. This included providing a glimpse into how volunteer lists were compiled throughout CDC by skill levels; how protocols for monitoring and managing laboratory testing were developed; and how internal and external communication lines were established. Dr. Nicholson also described how NCID laboratories rapidly expanded their space and capacity to handle the numerous challenges encountered in processing and testing the large, and sometimes unpredictable, influx of diverse specimens. She complimented the many volunteers who worked long hours to provide the multitude of skills and 24 hour/7 day a week coverage the EOC and laboratories required. In closing, Dr. Nicholson shared the lessons learned and summarized what needs to be done to prepare for future events, emphasizing the imminent need to plan using real scenarios from the anthrax event.

Committee Discussion

- CLIAC members recognized and applauded CDC's rapid response and heroic efforts in meeting the challenges of this unprecedented public health emergency.
- Several members asked how CDC plans to address the types of specimen tracking challenges encountered during the anthrax investigations. Dr. Nicholson indicated a field module, a hand-held device, has been developed for outbreak situations. This module provides menus for logging samples/specimens and selecting couriers, and includes a mechanism to alert laboratories to the expected time of sample/specimen arrival. She

- said a barcode labeling system still needs to be developed for field use.
- One member asked how laboratorians outside CDC could volunteer in the event of future incidents or outbreaks. Dr. Nicholson indicated a mechanism, including a personnel database, needs to be developed. The database should include both private-sector and government employees and provide information such as laboratory skills, availability, and the necessary work clearances.
 - Another member stated that many Level A laboratories felt disenfranchised and would have been willing to help. Dr. Nicholson emphasized there is a system in place for outbreak response that works. Protocol indicates specimens and questions should first go to the local public health facility, then to the state public health laboratory. CDC then works with the state public health laboratory. Many of the challenges encountered during the anthrax investigations arose when this system was by-passed and specimens sent directly to CDC.
 - When asked about the questions CDC received from the public, Dr. Nicholson responded the agency was overwhelmed with questions. All information released to the public had to be cleared first and it was sometimes difficult to provide timely and complete responses.
 - CLIAC members acknowledged the need to remain focused on the importance of building and maintaining a strong public health infrastructure that can respond rapidly to outbreaks and catastrophic events.

Towards a National Laboratory System

Addendum F

Dr. John Ridderhof, DLS, PHPPO, CDC, began his presentation by describing the current network of laboratories performing tests of public health significance (such as agents of bioterrorism, tuberculosis, HIV, blood lead) as a loose association of public health, hospital, and independent laboratories throughout the country where collaboration and communication is often inconsistent. He referenced several independent government reports identifying the lack of proactive federal leadership as contributing to the weaknesses identified in the nation's public health surveillance system. In response, CDC's Office of Laboratory Systems Development, within DLS, PHPPO, has developed strategic initiatives utilizing professional organizations, federal partners, and federally-funded state projects to assess laboratory capabilities, address gaps in training, establish uniform standards of laboratory practice, and improve collaboration of laboratories at the local level. Dr. Ridderhof closed by urging CLIAC support for DLS strategic initiatives to develop a National Laboratory System to assure consistent laboratory capacity for public health response across the nation.

Committee Discussion (See discussion following next presentation)

Dr. Lawrence Sturman, CLIAC member and Director, Wadsworth Center, New York State Department of Health, presented an overview of the Wadsworth Center's experience with environmental anthrax threats. Dr. Sturman began by reporting that from 1943 to 1960, most of the state's human anthrax cases involved workers in the carpet and leather industries, with the last reported case in 1961. He then shared with CLIAC some of the problems faced and the lessons learned as a result of the bioterrorism events of 2001.

Dr. Sturman first outlined the organizational structure of the Wadsworth Center and reviewed the design of its biosafety level-3 laboratory. He then provided data on the number of environmental samples received, described the varied packaging and unique sample types, and cited sample accessioning and tracking as major problems needing to be addressed. Dr. Sturman noted, of the more than 900 samples submitted for testing since October 2001, some were of valid concern with 24 testing positive for anthrax. However, the vast majority of the samples received, which included paper currency and clothing, were the result of hoaxes and/or public hysteria. He also recounted the Center's problems with and lack of preparedness for handling and testing a multiple/mixed agent hazard, a possible weapon of mass destruction in the future.

Dr. Sturman stressed integrated state and national response capabilities and capacities must be developed before they are actually needed. He concluded by sharing New York State's recommendations for BT laboratory preparedness, which address laboratory design and functions; a triage system and protocols for specimen/sample handling, tracking, and testing; and a result reporting system.

Committee Discussion (combined for both Dr. Ridderhof's and Dr. Sturman's presentations)

- Members agreed the anthrax threat was a "wake up call," clearly illuminating the need to improve the current public health laboratory infrastructure and develop lines of communication between regional and local laboratories. Members also concurred efforts in this regard must be sustained and long-term; it is imperative that federal support and funding not dissipate over time. With this in mind, the Committee requested a letter to the Secretary of HHS be developed expressing the Committee's support of NLS efforts **(Addendum H)**.
- The Committee discussed the necessity of collaboration among public, private, and government agency laboratories on technical knowledge and experience in test methodologies and development. This is essential to ensuring universal test availability, validation, and standardized utilization, as well as appropriate post-test counseling and follow-up. However, one member pointed out the advantage of having laboratories using different testing methodologies rather than all laboratories using the same method; it increases the likelihood of detecting an organism.
- Several members emphasized the importance of communication among local, state and federal public health agencies and private laboratories. They also stressed the necessity for data interchange standards. One member cited the National Cancer Institute-funded

Pathology Informatics Demonstration Project as an example, and asked if there is a similar laboratory data interchange standard that has achieved a broad consensus. Dr. Ridderhof responded by describing the National Electronic Disease Surveillance System (NEDSS) as a model communication system. This system is being developed by CDC to assure accurate, complete, and timely reporting of data for outbreak detection by implementing national data standards for surveillance and reporting by state and local health departments to CDC. Eventually, it will become an Internet-based communications infrastructure integrating public health information and healthcare data systems.

- A suggestion was made to have NEDSS as an agenda item for the next CLIAC meeting.

■ **Waiver Recommendations**

Addendum I

Dr. Merlin re-introduced the recommendations made by CLIAC in a June 8, 2001, letter to FDA in response to its draft waiver guidance. Since FDA has withdrawn its draft guidance, he asked the Committee if it would like to readdress these recommendations in a letter to the Secretary of HHS as general recommendations to be used in rule-making relative to the waiver review criteria and processes. Committee discussion centered around the CLIA statute, as modified by the FDA Modernization Act of 1997 (FDAMA), which automatically waives all tests approved by the FDA for home use. In particular, members continue to be concerned about the lack of uniformity in the two routes for waiver approval, that is, FDA's criteria for home use approval and the CLIA review criteria for waiver approval. FDA's home use approval criteria do not include a threshold for accuracy, which is a criterion under CLIA (accuracy is used to demonstrate low risk of an erroneous result), and home use approval does not consider the expanded use of these products in the clinical setting when they are waived. The Committee agreed its letter of June 8, 2001, should be readdressed to the Secretary and references to the draft waiver guidance eliminated. They emphasized the letter should include a recommendation that a statutory change be pursued, as needed, to ensure that all waived products are simple and have an insignificant risk of an erroneous result when used in clinical settings.

■ **Unregulated Tests Workgroup Report**

Addendum J

Dr. Barbara Goldsmith reported on the deliberations of the August 8, 2001, Unregulated Tests Workgroup meeting. During this meeting, the workgroup discussed possible criteria for determining whether CLIA should apply to breath tests and other currently unregulated tests. This included considering whether there are any unique testing contexts for which CLIA regulation is not appropriate. Workgroup members also discussed the value of CLIA oversight as well as the impact of regulations. They questioned if professional organizations' voluntary guidelines and standards are adequate to ensure quality testing, especially in nontraditional

testing sites. They also questioned whether it would be appropriate to create a new CLIA category for this type of testing with unique requirements for personnel qualifications, quality control, etc. Alternatives to CLIA regulation, such as encouraging professional organizations and manufacturers to develop standards and guidelines for testing as well as strengthening existing voluntary guidelines and standards, were also considered .

Committee Discussion

- There was much discussion as to whether this testing falls under CLIA regulation. One member suggested separating physiological tests from laboratory tests and considering only in-vitro tests using specimens that are tested in the laboratory (i.e., removed from the body for testing) as laboratory procedures. Dr. Goldsmith acknowledged the difficulty involved in separating these physiological procedures from laboratory tests.
- Dr. Gutman was asked how the FDA makes decisions as to whether devices are in-vitro or in-vivo and how FDA determines which Center has review responsibility. Dr. Gutman replied the process at FDA has evolved and there is not a specific algorithm.
- One member stated some tests, even if physiological, should fall under some type of oversight. This member continued, suggesting if CLIA were to recommend that voluntary standards be followed, it may be helpful to the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) and could influence compliance with practice guidelines and voluntary standards.
- The Committee's industry representative commented hospital quality/accreditation systems could address some of these concerns and a letter to CMS, the agency responsible for hospital certification, may be the best approach.
- Several members expressed caution in advancing into areas not stipulated by CLIA. They felt professional organizations representing pulmonary, cardiovascular, and radiological services/medicine would have more authority and credibility and are in a better position to develop standards of practice.
- Dr. Merlin stated that while much of the concerns about unregulated testing is really a "quality" issue, all aspects of medical care cannot be addressed by CLIA. He suggested the Quality Institute, tentatively planned for Spring 2003, may be a good forum for this discussion.
- In discussing breath testing, one member commented that breath is a specimen source and there is technological development occurring in this area. For example, devices are being developed that may be able to use breath to evaluate renal or urinary tract infection. This member felt that at minimum, results from these devices should correlate with laboratory tests.
- Dr. Merlin proposed that a breath specimen, when taken from a patient, then transported to the laboratory for testing, should be subject to CLIA. A member noted the breath could be collected from the patient, with testing performed at the bedside, while another member cautioned this could quickly move into regulating anesthesiology.
- Dr. Martin reminded the Committee that technology is rapidly evolving and some can provide measurements without removing substances from the body. He cited laser technology for non-invasive glucose and bilirubin determinations as an example. He

asked whether CLIA should also address this testing, even though a specimen is not removed from the human body and taken to the laboratory. Ms. Whalen advised that for this testing to be regulated under CLIA it would have to go through rule-making, and Ms. Coppola added, this may need a legal decision, since the CLIA statute pertains to a specimen “derived from the human body.”

- Members agreed these issues will remain on the horizon with the development of more non-invasive testing that is performed outside of the traditional laboratory.
- After much discussion, a motion was made and seconded to include breath, when derived from the human body and tested in a laboratory as defined by CLIA (“...a facility for the biological, microbiological, serological, chemical, immuno-hematological, hematological, biophysical, cytological, pathological, or other examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of human beings.”), as a specimen source under CLIA.

■ **Public Comments**

Addendum K

Mr. Phillip Bongiorno, representing the College of American Pathologists (CAP), addressed the Health Insurance Portability and Accountability Act (HIPAA) and its potential impact on CAP's accreditation activities performed as a deemed organization under CLIA. He stated HIPAA defines accreditation organizations and entities such as CAP as "business associates" rather than as "health oversight agencies." According to CAP, an accrediting organization would be required to execute a written "business associate" agreement with each laboratory it accredits. Mr. Bongiorno claimed establishing written agreements with each laboratory is burdensome and costly to both CAP and the laboratory and does not add any assurances relative to the privacy of patient information. In that HHS is currently drafting modifications to the final HIPAA privacy rule, CAP asked that CLIAC express support by letter to HHS recommending CAP, in its role as a deemed organization, be recognized in the final rule as a "health oversight agency" and thus, not subject to the "business associate" requirements.

Committee Discussion

- One member reminded the Committee that CAP activities are not limited solely to its deemed status activities relative to the accreditation of laboratories under CLIA and questioned whether there might be unintended consequences from designation of the CAP as a “health oversight agency.”
- Most members expressed concern about the apparent undue burden of HIPAA on deemed laboratory accreditation organizations acting on behalf of CMS. CLIAC proposed a letter to the Secretary expressing its concerns, but asked for CDC and CMS legal counsel review prior to proceeding.
- Members acknowledged having limited knowledge on HIPAA and suggested a future CLIAC agenda item address HIPAA and its impact on CLIA.

Dr. Joe Boone, DLS, PHPPPO, presented plans for a fifth critical issues conference, the Quality Institute, to be held in Atlanta mid-late April 2003. Previous conferences were held in 1984, 1986, 1989, and 1995. The purpose of this conference will be to develop a framework for a national report on the health laboratory system. The report will define the nation's laboratory system and a set of quality indicators for the system. Dr. Boone noted while there are many good efforts toward quality in existence, they are not connected. This institute would provide the opportunity for connection. Some of the project areas for the institute are: making the laboratory a partner in patient safety; developing quality indicators for laboratory personnel shortages; and developing an integrated approach to laboratory testing of public health importance. The conference will include plenary sessions, workgroups, and poster sessions. It is hoped an ongoing Quality Institute will be created to foster continuous data collection and analysis with dissemination of this information via the Internet for use by legislators, patient advocacy groups, clinicians, etc.

Committee Discussion

- One member suggested the Quality Institute look at developing data on workforce shortages and whether there is correlation with the frequency of laboratory errors, which result in poor patient outcomes. Others questioned how to collect risk-management data organizations gather but are reluctant to release. One issue to consider is whether errors occur because of unqualified personnel or overworked staff, or are the errors due to poor management. Another member added the relationship between the clinician and the laboratorian should be considered. In some cases, the knowledge of the laboratorian about testing services exceeds that of the laboratory user.
- Dr. Boone replied the difficulty in gathering laboratory/medical error information may be a social and legal problem. Our society tends to assign blame and punish rather than identify and address the problem. We need to get past a punitive viewpoint and change to one of problem identification and correction.
- The Committee's industry representative stated the Medical Device Reporting regulations require manufacturers to report deaths, hazards, and events to the government. Manufacturers are held accountable and are not provided confidentiality when reporting errors. Improvements in industry have occurred when manufacturers evaluate errors and use the information to make better products. She added, this reporting requirement needs to be extended to hospitals and other healthcare settings for quality improvement purposes.
- Dr. Merlin stated JCAHO attempted to require participating institutions to report incidents, but the institutions persuaded JCAHO to reconsider this requirement because of concerns over liability. Without a major change with respect to protection, voluntary reporting does not seem to be workable.
- One commenter suggested we need to find a way to gain Congressional support for making the changes necessary to allow institutions and organizations to share data without fear of liability.

- The Committee strongly supported the concept of a Quality Institute and expressed the need for a systematic approach for looking at quality and translating it into a sustainable process. They noted good data are needed to formulate good policies and agreed this forum could serve as a stepping stone to gather such data. A balance between access and quality must be achieved.

■ **Secretary's Advisory Committee on Genetic Testing (SACGT) Meeting Report**

Addendum M

Dr. Patricia Charache, CLIAC member and Program Director, Quality Assurance and Outcomes Assessment, Johns Hopkins Medical Institutions, summarized the focus and activities of the SACGT from 1999 through 2001. She related the progress of the five SACGT workgroups on data collection, education, rare disease testing, access, and informed consent and institutional review boards (IRBs). She also updated CLIAC on the development and pilot testing of an FDA pre-market review template for new genetic tests. Dr. Charache highlighted activities of the SACGT workgroups, as listed below.

Data Workgroup

The goal of this workgroup is to increase knowledge relative to the clinical utility of genetic tests through improved data collection and analysis. SACGT is concerned about several issues related to data collection: the definition of a “test”; mechanisms to obtain both clinical and laboratory data; privacy and costs of data collection efforts; and approaches of secondary data synthesis. Thus far, a cooperative agreement between CDC and the Foundation for Blood Research has evaluated three common genetic tests and has developed a framework for analyzing the validity and utility of genetic tests.

Education Workgroup

This workgroup held a roundtable meeting in November 2001 to consider the needs and appropriate approaches to providing genetics education to healthcare professionals, patients, and other users of genetic testing services. SACGT is planning a two-day workshop in May 2002, entitled “Genetic Testing and Public Policy: Preparing Health Professionals,” to explore the integration of genetics into routine patient care and to address the needs for ensuring appropriate use of genetic tests.

Consent/IRB Workgroup

This workgroup has developed a brochure to serve as a model for explaining genetic testing and informed consent to the general public. The workgroup is also preparing a white paper on principles, content, and level of informed consent for different types of genetic tests. However, SACGT acknowledged it is outside its purview to define the specific type of consent needed for each test. The workgroup is concerned with defining the role of professional organizations, FDA, and laboratories in assuring appropriate informed consent for genetic tests.

Rare Disease Testing Workgroup

The goal of this workgroup is to develop knowledge of and access to quality testing for rare diseases. Dr. Charache briefly outlined the presentations by representatives of academic research laboratories, commercial genetic testing laboratories, FDA, and the National Institutes of Health at the November 2001 SACGT meeting. She pointed out some approaches proposed to SACGT were illegal, such as allowing research laboratories (not CLIA-certified) to perform patient testing and report negative results, if confirmatory testing is provided by a CLIA-certified laboratory.

Access Workgroup

This workgroup focused on issues centering around access to genetic testing such as the patient's need for information; reimbursement issues; and the impact of patents on access to and quality of testing. Some of the reimbursement issues addressed were the views of payers, test costs (including the large number of non-reimbursed laboratory costs), and counseling needs and costs.

Committee Discussion

- Several members expressed concerns about the complexity of collecting and analyzing genetic testing data; the need to address quality assurance issues for patient testing offered by laboratories that primarily conduct research; and appropriate approaches to assuring informed consent for genetic tests.
- One member commented that establishing the validity and utility of genetic tests is more complicated than addressed by the Data Workgroup, since the relationship of genes and diseases are complex and true single-gene disorders may not exist.
- Another member expressed concern about the over-simplification of the terms used in the data collection projects presented to SACGT, as the clinical significance of a genetic alteration is sometimes unclear and genotype-phenotype correlation is often complex. This member commented on the inability of those terms to capture the richness and complexity of genetic tests. Dr. Charache responded these comments were appreciated and would be conveyed to SACGT.
- Several members recommended developing approaches allowing research laboratories to offer rare disease testing while complying with federal and state laws. One member commented that such approaches are needed, particularly since researchers may be requested to release test results to research subjects. Another member suggested academic institutions should be involved in the development of appropriate approaches.
- Regarding informed consent for genetic tests, one member noted informed consent is required for every laboratory test and is dictated by state-based case law, rather than statutes. Another member suggested genetics professional organizations should be involved in defining appropriate informed consent and the role of health professionals and laboratories in obtaining this consent. In addition, concern was expressed that requiring informed consent through the FDA test review process might not be the best approach.

- Dr. Boone suggested CLIAC consider potential non-regulatory approaches to ensuring informed consent for genetic testing, as it might not be possible to solve medical practice issues through regulation. He also noted several patient advocacy groups, concerned with the appropriateness of documenting patient consent by check-boxes, have requested that patient signatures be required for all genetic tests. Dr. Charache responded that a white paper under development by the Consent/ IRB Workgroup would allow flexibility by recommending a gradient of informed consent requirements for different types of tests. She further suggested that a CPT code might be needed to reimburse laboratories for the work entailed in contacting clinicians to ensure patient consent has been obtained.

■ **IVD Regulation Overview**

Addendum N

Ms. Kay Setzer, CLIAC Advanced Medical Technology Association liaison, provided an overview of in-vitro diagnostic (IVD) statutory and regulatory requirements. She focused on the Quality System Regulation, which governs manufacturers, and emphasized that the company's senior management is accountable for the establishment and maintenance of an effective Quality System that addresses planning, commitment, actions, and follow-up. She also reviewed the FDA's PMA and 510(k) review processes. The key points in her presentation were IVD's are subject to regulation under numerous statutes; the manufacturer is required to maintain a Quality System that is audited by the FDA for all devices; and higher risk devices require submission of more supportive information to demonstrate safety and effectiveness.

Committee Discussion

- One member questioned how one manufacturer evaluates another manufacturer when considering the company for purchase. Ms. Setzer replied a very careful quality system review and evaluation is performed to evaluate the company prior to purchase. Another member acknowledged the increased quality of products on the market today, complimenting the IVD industry and FDA's efforts and commitment in this regard.
- Dr. Gutman was asked what qualifies a product as exempt from PMA or 510(k) review. Dr. Gutman replied exemption is based on low risk. As background, most Class I and many Class II devices considered to be low risk are exempt from the premarket notification requirements under FDAMA. In addition, some Class III devices (subject to PMA review) have been down-classified to Class II with a 510(k) review because the risk is considered to be lower than a PMA review warrants. However, the law still requires PMA review of a new device with no predicate device for comparison, even if it is simple.
- One member expressed concern with the inclusion of QC materials and several immunological products on FDA's exemption list. Ms. Setzer replied that even though these products are exempt from submission, they still require design controls and all products are required to meet cGMP. In addition, these data must be available for inspection by FDA.

- One member asked how a device is down-classified. Dr. Gutman responded this generally begins with a request from the manufacturer, with data to support the request, but can also be initiated by FDA during the review process.

■ **Public Comments**

Addendum O

Ms. Karen Hickey, Vice President, Regulatory and Clinical Affairs, Binax, Inc., recounted the company's experiences with the CLIA waiver process during the transition of waiver responsibility from CDC to FDA. Binax submitted waiver applications for two products in 1998 and 1999, and the respective waiver determinations are still pending. She requested the Committee, as it provides advice and guidance relative to the waiver regulation under development, to consider the impact on manufacturers and the benefit to public health.

■ **Adjourn**

Dr. Merlin adjourned the meeting. The next CLIAC meeting is scheduled for September 11-12, 2002.

I certify that this summary report of the January 30-31, 2002, meeting of the Clinical Laboratory Improvement Advisory Committee is an accurate and correct representation of the meeting.

/s/ Toby Merlin, M.D., CLIAC Chair

Date: April 10, 2002